22. The DNA according to claim 13, wherein said first protein or protein domain comprises CpTI.

23. An isolated DNA molecule encoding a linker peptide, wherein said linker peptide comprises at least one of SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:11.

REMARKS

In the above-referenced Office Action, the Examiner rejected Claims 1-14 and 16-17 and withdrew Claim 15 from consideration as being drawn to a non-elected invention. Applicants thank the Examiner for partially withdrawing the restriction requirement of December 14, 2001 (Paper No. 10) and for examining the inventions of both Group I (Claims 1, 3-13, and 16-17) and Group II (Claims 2 and 14) in the present application. Applicants also thank the Examiner for acknowledging that the inventions recited in Claims 9-11 are free of the prior art, given the failure of the prior art to teach or suggest a method of improving pathogen resistance or tolerance in plants by transformation with a DNA molecule that encodes a fusion protein comprising two anti-pathogenic proteins or protein domains joined by the linker peptide of SEQ ID NOs:1, 2, or 11.

With entry of this Amendment, claims 1, 2, 4-11, 13, 14, and 16 are pending. Claims 1, 2, 4-8, 13, 14, and 16 are amended herein. Support for the amendments may be found throughout the specification, and particularly at pages 2-3, 8-9 and 16-22, and in the original claims.

Objections to the Specification

The Examiner objects to the title of the application as not being descriptive of the claimed invention. Applicants respectfully submit that the title, as amended herein, is clearly indicative of the invention to which the elected claims are drawn. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

The Examiner next states that the application does not contain an abstract of the disclosure and requires that an abstract be submitted on a separate sheet. Applicants submit that an abstract in compliance with 37 C.F.R. § 1.72(b) is enclosed herewith. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

The Examiner next objects to the specification as containing sequences that are not accompanied by SEQ ID NOs (*e.g.*, page 17, line 3), as required by 37 C.F.R. §§ 1.821 through 1.825. Applicants respectfully submit that the specification is amended herein to include appropriate references to two SEQ ID NOs (*i.e.*, SEQ ID NOs: 1 and 2) after two amino acid sequences presented on page 17 (*i.e.*, lines 3 and 12, respectively). These SEQ ID NOs are already listed in the sequence listing but were inadvertently omitted after the sequences noted on page 17. The undersigned believes that the specification, as amended herein, is now in full compliance with the sequence rules. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

Rejection under 35 U.S.C. § 101

Claim 17 stands rejected under 35 U.S.C. § 101 because the claimed recitation of a use, without setting forth any steps involved in a process, allegedly results in an improper definition of a process. Applicants respecfully submit that since Claim 17 is cancelled herein, this rejection is rendered moot.

Claims 13-14 and 16 stand rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. Applicants respectfully submit that Claim 13 is amended herein to recite "An isolated DNA molecule", and Claim 16 is amended herein to recite "A transgenic plant", thereby obviating the rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112, ¶ 1: Written Description

Claims 1-14 and 16-17 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. (Office Action at page 4.) In particular, the Examiner contends that the specification does not describe, within the full scope of the claims, DNA molecules that encode a fusion protein comprising two anti-pathogenic proteins joined by a linker peptide. Applicants respectfully traverse this rejection.

As stated in MPEP § 2163(II)(A), "The examiner has the initial burden ... of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims." That burden cannot be satisfied by mere conclusary statements. Applicants respectfully submit that the Examiner has offered insufficient reasons as to why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.

Contrary to the Examiner's assertion, the instant specification adequately describes the claimed invention and clearly allows persons of ordinary skill in the art to recognize that Applicants invented the claimed subject matter. Some of the relevant teachings of the instant specification are discussed further below.

The Examiner asserts that the "specification only describes coding sequences that encode Oc-I, Oc-IΔD86 and CpTI and linker peptides of SEQ ID NOs:1, 2 and 11." (Office Action at pages 4-5.)

Applicants respectfully disagree. In fact, Applicants' specification explicitly teaches that other anti-pathogenic proteins or protein domains, including for example, known proteins or protein domains noted in the specification (see, *e.g.*, Specification, p. 6, lines 15-22), are contemplated by the claimed invention.

Moreover, the Examiner is reminded that, notwithstanding *In re Shokal*, a specification can provide an adequate written description of a claimed invention under § 112 without describing all species encompassed by the claim invention. As the Office has stated in its very own Guidelines, "there is no basis for a *per se* rule ... limiting DNA claims to only the sequence disclosed". (Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, "Written Description" Requirement, Response to Specific Comment 9, 66 Fed. Reg. 1099, 1101.)

The Examiner further asserts that "Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided." (Office Action at page 5.) Again, Applicants respectfully disagree. The Office has indicated that a proper determination of whether the written description requirement is satisfied necessitates a reading of the disclosure in the light of the knowledge possessed by those of skill in the art at the time of filing. MPEP § 2163 II.A.2.

As Applicants pointed out above, the specification teaches a hosts of protein and protein domains that are contemplated by the claimed invention. DNA molecules encoding such proteins were known in the art prior to the effective filing date of the instant application. For example, DNA encoding a proteinase inhibitor from *Manduca sexta* is disclosed in U.S. Patent No. 5,436,392 (attached hereto as Exhibit A), which issued July 25, 1995 (see SEQ ID NO: 1); DNA encoding an insecticidal protein is disclosed in U.S. Patent No. 5,461,032 (attached hereto as Exhibit B), which issued October 24, 1995 (see SEQ ID NOs: 2 and 4); and DNA encoding a synthetic *Bacillus thuringiensis* toxin is disclosed in U.S. Patent No. 5,380,831 (attached hereto as Exhibit C), which issued January 10, 1995 (see FIG. 1). As acknowledged by the Examiner, the specification also teaches DNA sequences encoding linker peptides of the claimed invention.

The facts in the instant case are distinguishable over the facts in *University of California v. Eli Lilly* and *Amgen v. Chugai Pharmaceutical Co. Ltd.*, which were cited by the Examiner. In the instant case, sequences of the claimed DNA molecules are

known; in the cases cited by the Examiner, the claimed DNA sequences were not known.

Finally, Applicants note that this rejection is moot with respect to claim 17 since the claim has been cancelled.

For the reasons set forth above, Applicants submit that the instant application provides sufficient written description for the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, ¶ 1: Enablement

Claims 1-14 and 16-17 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. (Office Action at page 6.) While acknowledging that the specification is enabling for a method of improving the nematode resistance of a plant by transformation with a DNA construct encoding the protease inhibitors Oc-IΔD86 and CpTI joined by the linker peptide of SEQ ID NOs:1, 2, or 11, the Examiner contends that the specification does not enable one skilled in the art to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

In particular, the Examiner states that the "instant specification fails to provide guidance for use of DNA constructs encoding anti-pathogenic proteins of any size or linkers of any size." (Office Action at page 7.) The Examiner asserts that not all proteins are small enough to be ingested by nematodes and concludes that "DNA constructs encoding fusion proteins that are too large will not be effective in the instant method." *(Id.)*

Applicants respectfully remind the Examiner that "the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard, as set forth by the Office, is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in

the art." MPEP § 2164.08(b). The Examiner has presented no evidence showing that the effort required for the skilled artisan to determine which embodiments were conceived in the instant case is more than is normally required in the art. Absent such a showing, lack of enablement has not been established in the instant case.

In any event, Urwin *et al.*, the very reference cited by the Examiner to support his position, shows that one skilled in the art would have been aware that "the size of the effector molecule is an important consideration in an anti-feedant strategy." (Urwin *et al.*, p. 459, left column, para. 3.) Moreover, as Urwin *et al.* demonstrates, those skilled in the art would have known, for example, that *M. incognita* can ingest proteins of at least about 28 kDa, while H. *schachtii* cannot ingest a protein of that size. *Id.* Thus, the level of skill in the art at the time of filing was such that the skilled artisan would have been aware that, depending upon the specific pathogen selected, there might be an upper limit to the size of any particular fusion protein encoded by a DNA construct prepared in accordance with the claimed invention.

The Examiner further asserts that "protease inhibitors, when expressed in a plant, do not provide resistance to all pathogens." (Office Action at page 7.) However, Applicants respectfully submit that the claimed invention is not limited to protease inhibitors. Independent Claims 1 and 13, for example, each recite "protein, or protein domain, with anti-pathogenic activity". Moreover, while Applicants' specification teaches anti-pathogenic proteins or protein domains that include protease inhibitors, the specification also teaches that anti-pathogenic proteins or protein domains other than protease inhibitors, such as, for example, any of the several types of known proteins or protein domains noted in the specification (p. 6, lines 15-22), may be used in the practice of the claimed invention. Applicants submit that the level of skill in the art at the time of filing was such that the skilled artisan would know to employ particular anti-pathogenic proteins or protein domains to regulate a particular pathogen. Indeed, this is made clear by Gleddie *et al.*, a reference cited by the Examiner, which states,

> "... it appears obvious that the development of any pathogen control strategy based on recombinant PIs must be adapted to each particular plant-pathogen system, and that the PIs must be chosen with care for each

> particular protease or group of proteases to be regulated." Gleddie *et al.*, "The Control of Plant Pathogens with Protease Inhibitors: A Realistic Approach?", *in*: Recombinant Protease Inhibitors in Plants, Michaud, ed., pp. 53-64 (2000); see p. 59, left column, para. 2.

This conclusion by Gleddie *et al.* was based upon research that predates the priority date (December 3, 1997) of the instant application (*i.e.*, see p. 59, left column, paras. 1 and 2 and corresponding notes 28-31, noting publication dates of 1995 and 1996).

The Examiner also contends that the specification fails to teach the appropriate cellular targeting of the encoded fusion protein and cites Gleddie *et al.* (p. 60, left column, para. 2) in support of this contention. Applicants respectfully submit that Gleddie *et al.* merely speculates that protease inhibitors should be "translocated to the appropriate cellular location, usually to the extracellular compartment for fungi and bacteria, or to the cytoplasm for viruses." *Id.* at lines 10-13. Moreover, Gleddie *et al.* discusses only protease inhibitors and discusses them with reference to certain broadly characterized pathogens (fungi, bacteria, and viruses). Gleddie *et al.* makes no mention of any other types of anti-pathogenic proteins or protein domains, nor does Gleddie *et al.* refer to pathogens such as nematodes, insects, mites, and the like. As taught by the instant specification (see, *e.g.*, p. 1, lines 9-10), the claimed invention may be used to provide resistance or tolerance to these forms of pathogens.

The Examiner asserts that "the specification fails to provide guidance for improving the resistance of a plant to any pathogen." (Office Action at page 7.) The Examiner also asserts that "undue trial and error experimentation would be required to screen through the myriad of DNAs that encode proteins with anti-pathogenic activity, and plants transformed therewith, to identify those that confer increased pathogens resistance against the multitude of different pathogens as claimed." (Office Action at paragraph bridging pages 7 and 8.)

It is well-established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 736-737 (Fed. Cir. 1988). In fact, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with

respect to the direction in which the experimentation should proceed." *Id.* at 737 (internal citation omitted).

Applicants respectfully submit that the Examiner has not established that the state of the art was such that undue experimentation would be required to prepare a DNA molecule encoding a fusion protein comprising proteins or protein domains other than Oc-IΔD86 and CpTI.

Moreover, Applicants submit that the instant specification provides sufficient guidance regarding the generation of DNA expression cassettes (Examples 1 and 2) and that these Examples along with the additional guidance provided in other portions of the specification, coupled with a knowledge in the art of standard procedures for screening, making, manipulating, and analyzing DNA, would have enabled one skilled in the art to make and use Applicants' invention in a manner that was commensurate in scope with the claims.

Applicants therefore submit that, in view of the teachings of the specification and the state of the art at the time of filing, it would have routine for one skilled in the art to actualy obtain variants of the exemplified DNA molecules by selecting a pathogen (such as, for example, any of the types set forth in the specification at p. 6, lines 21-22), selecting two proteins or proteins domains that are known to be effective against that pathogen, isolating the DNA molecules encoding those proteins or protein domains, and then linking them together with the claimed linker peptide.

For the foregoing reasons, Applicants respectfully submit that the instant specification, coupled with what was known in the art at the time of filing, would have provided sufficient guidance to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation.

Applicants respecfully submit that since Claim 17 is cancelled herein, this rejection is rendered moot as to that claim.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, as applied to claims 1-14 and 16.

Rejection under 35 U.S.C. § 112, ¶ 2

Claims 1-14 and 16-17 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. (Office Action at page 8.) Applicants respectfully traverse this rejection.

Regarding Claims 1-12, the Examiner states that the claims are indefinite because they lack agreement between the preamble to the method claims and the positive method steps. The Examiner contends that methods must be circular and that "the final step must generate the item that the method is intended to produce." Office Action, page 8. Applicants respectfully disagree with the Examiner. Specifically, method or process claims may be of at least three types: generalized methods for accomplishing some specified end, methods of use, and product-by-process. See, *e.g.*, MPEP § 2112.02. Applicants respectfully submit that, unless a method claim is a product-by-process claim, there is no requirement of which Applicants are aware that a method must be "circular", such that the final step generates a product or item. Applicants' independent Claim 1 recites "A method of improving resistance or tolerance in a plant and its descendant plants to a pathogen". The claimed method does not require that a product or item be produced. Applicants therefore respectfully submit that there is no requirement for a final step that generates a product or item.

Regarding Claims 1 and 13, the Examiner states that the claims are indefinite because it is not clear whether the recitation of "with anti-pathogenic activity" in parts (a) and (c) is intended to modify both "protein" and "protein domain" or whether it is intended to modify only "protein domain". Applicants respectfully submit that, solely for the sake of ensuring clarity, the claims are amended herein to recite "protein, or protein domain,

with anti-pathogenic activity", which makes clear that "with anti-pathogenic activity" modifies both "protein" and "protein domain", thereby obviating the rejection.

Regarding Claim 6, the Examiner states that it is not clear whether the recited promoter refers to the one that is a part of the gene or whether it refers to another promoter, in addition to the promoter that is part of the gene. The Examiner notes that the term "gene" refers to a DNA that comprises a promoter and a coding region. Applicants respectfully submit that Claim1, as amended and no longer recites the term gene, thereby obviating this rejection.

Regarding Claim 12, the Examiner contends that the claim makes no sense as written. Claim 12 has been cancelled, thereby rendering this rejection moot.

Regarding Claim 13, the Examiner states that the claim is indefinite in its recitation of "capable of", as it is not clear that the DNA molecule actually does encode the fusion protein. Applicants respectfully submit that Claim 13 is amended herein and not longer recites the phrase "capable of."

Regarding Claim 14, the Examiner states that the claim lacks antecedent basis for the limitation "the encoded fusion protein" in line 1. Applicants respectfully submit that dependent Claim 14 is amended herein to recite "said fusion protein", which finds antecedent basis in line 1 of independent Claim 13, which recites "a fusion protein".

Regarding Claim 17, the Examiner states that the claim is indefinite because it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Applicants respectfully submit that Claim 17 is cancelled herein, thereby rendering this rejection moot.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the claim rejections under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 102

Claim 13 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Warren *et al.* (WO 96/10083). (Office Action at page 10.) The Examiner states that

Warren *et al.* teach a maize-optimized DNA molecule encoding the anti-pathogenic proteins VIP2A(a) and VIP1A(a) linked by a linker peptide (p. 93). Applicants respectfully traverse this rejection.

Claim 13 is directed to an isolated DNA molecule encoding a fusion protein, wherein said fusion protein comprises (a) a first protein, or protein domain, with anti-pathogenic activity; (b) a linker peptide; and (c) a second protein, or protein domain, with anti-pathogenic activity, wherein at least one of the proteins or protein domains with anti-pathogenic activity has proteinase inhibitor activity. Warren *et al.* does not disclose, *inter alia*, an isolated DNA molecule encoding a protein or protein domain having proteinase inhibitor activity. Thus, each and every element of Claim 13 is not disclosed by Warren *et al.* Accordingly, Warren et al. does not anticipate Claim 13. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Claims 1-3, 7, 12-14, and 16-17 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Anderson *et al.* (WO 94/13810). (Office Action at page 10.) The Examiner contends that Anderson *et al.* teach a nucleic acid encoding a type II serine protease inhibitor from *Nicotiana alata*, which contains 6 reactive domains. The Examiner further contends that these domains are joined by linkers, noting FIG. 1 and pp. 26-27. The Examiner further contends that Anderson *et al.* also teaches a method of using this nucleic acid to increase resistance of a plant to insects or other pathogen infestations as well as teaching plants so transformed. Applicants respectfully traverse this rejection.

Claim 1 as well as the rejected claims dependent thereupon are directed to "A method of improving nematode resistance or tolerance in a plant and its descendant plants, the method comprising integrating into the genome of a plant a DNA molecule encoding a fusion protein, wherein said fusion protein comprises *inter alia,* a linker peptide. Claim 13 as well as the rejected claims dependent thereupon, are directed to "An isolated DNA molecule encoding a fusion protein, wherein said fusion protein comprises," *inter alia*, a linker peptide.

While the Examiner contends that Anderson *et al.* (FIG. 1 and pp. 26-27) discloses protein domains joined by linkers, there appears to be no reference to a linker peptide in either FIG. 1 or pp. 26-27. Moreover, Anderson *et al.*'s description of FIG. 1 states, "The *N. alata* PI sequence contains six similar doamins (domain 1, residues 1 to 58, domain 2, residues 59-116, domain 3, residues 117-174, domain 4, residues 175-232, domain 5, residues 233-290 and domain 6, residues 291-343" (p. 14). Since each domain is contiguous with the next, Applicants respectfully submit that Anderson *et al.* does not teach a linker peptide that joins two protein domains. Thus, Applicants submit that each and every element of independent Claims 1 and 13, and the rejected claims dependent thereupon, is not disclosed by Anderson *et al.* (WO 94/13810). Hence, the claims are not anticipated by Anderson et al. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Applicants respectfully submit that since Claims 3, 12, and 17 are cancelled herein, this rejection is rendered moot as to those claims.

Claims 1-3, 7, 12-14, and 16-17 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Anderson *et al.* (U.S. Pat. No. 6,031,087). The Examiner contends that Anderson *et al.* teach a nucleic acid encoding a type II serine protease inhibitor from *Nicotiana alata*, which contains 6 reactive domains. The Examiner further contends that these domains are joined by linkers, noting FIG. 1 and column 17, lines 12-39. The Examiner further contends that Anderson *et al.* also teach a method of using this nucleic acid to increase resistance of a plant to insects or other pathogen infestations as well as teaching plants so transformed. Applicants respectfully traverse this rejection.

Anderson *et al.* (U.S. Pat. No. 6,031,087) suffers from the same deficiencies as Anderson *et al.* (WO 94/13810). Thus, for the reasons stated above with respect to Anderson *et al.* (WO 94/13810), Applicants submit that each and every element of independent Claims 1 and 13, and the rejected claims dependent thereupon, is not disclosed by Anderson *et al.* (U.S. Pat. No. 6,031,087). Hence, the claims are not

anticipated by Anderson et al. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(e).

Applicants respectfully submit that since Claim 3, 12, and 17 are cancelled herein, this rejection is rendered moot as to those claims.

Claim 13 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Atkinson *et al.* (WO 96/16173). The Examiner contends that Atkinson *et al.* teach DNA constructs encoding the anti-pathogenic protease inhibitors chicken egg white cystatin linked to oryzacystatin joined by various linker peptides (pp. 22-24). Applicants respectfully traverse this rejection.

As stated above, Claim 13 is directed to "An isolated DNA molecule encoding a fusion protein, wherein said fusion protein comprises," *inter alia*, "a linker peptide." Atkinson *et al.* does not disclose such an isolaated DNA molecule. There is no teaching in Atkinson et al. of a DNA molecule encoding a fusion protein comprising a linker peptide. Thus, each and every element of Claim 13 is not disclosed by Atkinson *et al.* Accordingly, Claim 13 is not anticipated by Atkinson. Applicants therefore respectfully request recosideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Claim 13 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Mapelli *et al.* (EP 497,366). The Examiner contends that Mapelli *et al.* teach DNA constructs encoding mulitmers of anti-microbial proteins joined by a "bridge" or linker peptide (p. 5, line 51 to p. 6, line 11; Example 22). Applicants respectfully traverse this rejection.

Claim 13 is directed to an isolated DNA molecule encoding a fusion protein, wherein said fusion protein comprises (a) a first protein, or protein domain, with anti-pathogenic activity; (b) a linker peptide; and (c) a second protein, or protein domain, with anti-pathogenic activity, wherein at least one of the proteins or protein domains with anti-pathogenic activity has proteinase inhibitor activity. Mapelli *et al.* does not disclose an isolated DNA molecule encoding a fusion protein, wherein said fusion protein comprises, *inter alia*, a second protein, or protein domain, with anti-pathogenic activity,

wherein at least one of the proteins or protein domains with anti-pathogenic activity has proteinase inhibitor activity. Thus, Mapelli et al. does not disclose each and every element of Claim 13 and is not an anticipatory reference. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103

Claims 1-5, 7-8, 12-13, and 16-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Atkinson *et al.* (WO 96/16173) in view of Lilley *et al.* (1996, Parisitology 113:415-424). (Office Action at pages 11-12.) Applicants respectfully traverse.

The deficiencies of Atkinson et al., addressed above in response to the 102(b) rejection of Claim 13 are applicable here and therefore incorporated by reference herein. Atkinson et al. is deficient in that the reference neither teaches nor suggests, *inter alia*, an isolated DNA molecule encoding a fusion protein comprising a linker peptide, as required by the invention as claimed. The reference also fails to teach or suggest a transgenic plant expressing such a DNA molecule or methods of improving nematode resistance or tolerance in a plant and its descendant plants comprising integrating such a DNA molecule into a plant genome, as required by the claimed invention.

The deficiencies of Atkinson et al. are not remedied by Lilley et al. Since Lilley et al. suffers from the same deficiencies as Atkinson et al., the combination of Atkinson et al. with Lilly does not render the claimed invention obvious.

As the claims are patentable over the references, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

Applicants note that since Claims 3, 12, and 17 are cancelled herein, thereby rendering this rejection moot as to those claims.

Claims 1-8, 12-13, and 16-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Atkinson *et al.* in view of Hepher *et al.* (1992, EP 502,730) and Conkling *et al.* (U.S. Pat. No. 5,837,876). (Office Action at page 12.) Applicants respectfully traverse this rejection.

The deficiencies of Atkinson et al. are addressed in the preceding rejection under § 103(a). Hence the response above is incorporated by reference herein. The deficiences of Atkinson et al. are not remedied by the secondary references, Hepher et al. and/or Conkling et al. The cited references, considered alone or in combination, fails to teach or suggest the invention *as claimed.* Thus, Claims 1-8, 12-13, and 16 are not rendered obvious by Atkinson *et al.* in view of Hepher *et al.* and Conkling *et al.* Accordingly, Claims 1-8, 12-13, and 16 are patentable over the references. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Applicants note that since Claims 3, 12, and 17 are cancelled herein, thereby rendering this rejection moot as to those claims.

CONCLUSION

Pursuant to the foregoing remarks, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. § 112 and are allowable over the prior art of record. No new matter is added by this amendment. Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendment. The attached marked-up pages are captioned

"**Version With Markings To Show Changes Made**". Entry of the amendments is respectfully requested.

Respectfully submitted,

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Date: October 9, 2002

Version With Markings To Show Changes Made

In the Specification

The specification has been amended as follows:

On page 1, the title of the application has been amended to read as follows:

DNA Encoding Proteinase Inhibitor Fusion Proteins

The final paragraph on page 11, at lines 22-33, has been amended as follows:

Preferably, the [5¢ leader] 5' leader sequence is included in the expression cassette construct. Such leader sequences can act to enhance translation. Translation leaders are known in the art and include: picornavirus leaders, for example, EMCV leader (Encephalomyocarditis 5' noncoding region) (Elroy-Stein, O., Fuerst, T.R., and Moss, *Proc. Natl. Acad. Sci.* USA 86:6126-6130 (1989)); potyvirus leaders, for example, TEV leader (Tobacco Etch Virus) (Allison *et al.*, MDMV leader (Maize Dwarf Mosaic Virus); *Virology*, 154:9-20 (1986)), and human immunoglobulin heavy-chain binding protein (BiP), (Macejak, D.G., and Samow, P., *Nature* 353:90-94 (1991); untranslated leader from the coat protein mRNA of alfalfa mosaic virus (AMV RNA 4) (Jobling, S.A., and Gebrke, L., *Nature*, 325:622-625 (1987)); tobacco mosaic virus leader (TMV) (Gallie, D.R. *et al.*, *Molecular-Biology of RNA*, pages 237-256 (1989)); and maize chlorotic mottle virus leader (MCMV) (Lommel, S.A. *et al.*, *Virology* 91:382-385 (1991)). *See also*, Della-Cioppa *et al.*, *Plant Physiology* 84:965-968 (1987).

The first paragraph on page 17, lines 1-4, has been amended as follows:

(Ho et al, Gene 77: 51-59, 1989, and Horton et al, Gene 77 61-68, 1989) using primers P1 and P4. This results in Oc-IΔD86 and CpTI being separated by the cleavable linker with the amino acid sequence VIL GVGPA KIQ FEG (SEQ ID NO:1), where the arrows indicate putative cleavage sites (Oc-IΔD86 \PsMTa\ CpTI fusion protein).

The second paragraph on page 17, lines 5-12, has been amended as follows (inserted text is double-underlined to distinguish from the original underlined text):

A similar procedure is used to generate a DNA fragment encoding Oc-IΔD86 and CpTI with an intervening non-cleavable linker (Oc-IΔD86/go/CpTI fusion protein) obtained from the galactose oxidase gene sequence (McPherson et al. 1992) on the one hand using a primer [pairs] pair consisting of P1 above and P5 (5' – CTGGGGGGCTGTGTAAGAACTAGCTTGGGCATTTGCACTGGCATC-3'; SEQ ID NO:7) and on the other hand a primer pair consisting of P6 (5' – AGTTCT TACACAGCCCCCCAGCCTGGTAGTAATCATCATGATGAC- 3'; SEQ ID NO:8) and P4 above (sequence encoding the linker is underlined). This non-cleavable linker sequence encodes a peptide with the sequence QASSYTAPQPQ (SEQ ID NO:2).

In the Claims

Claims 3, 12, 15 and 17 have been cancelled without prejudice or disclaimer.

Claims 18-24 have been added.

Claims 1, 2, 4-8, 13, 14, and 16 have been amended as follows:

1. (Amended) A method of improving nematode [pathogen] resistance or tolerance in a plant and its descendant plants comprising:

integrating into the genome of said plant [a gene] a DNA molecule encoding a fusion [protein comprising] protein, wherein said fusion protein comprises:

(a) a first [protein or protein domain] protein, or protein domain, with anti-pathogenic activity;

(b) a linker peptide; and

(c) a second [protein or protein domain] protein, or protein domain, with anti-pathogenic activity, wherein at least one of the proteins or protein domains with anti-pathogenic activity has proteinase inhibitor activity.

9. (Amended) The method according to claim 1, wherein said fusion protein further comprises at least one additional protein or protein domain [proteins or protein domains with anti-pathogenic activity are] fused by at least one additional linker peptide to at least one of said first protein or protein domain, said linker peptide, and said second protein or protein domain [to the fusion protein by linker peptides].

4. (Amended) The method according to claim 3, wherein at least one of said first protein or protein domain and said second protein or protein domain [the proteins or protein domains with anti-pathogenic activity is the] comprises one of Oc-I and Oc-IΔD86 [proteinase inhibitor Oc-IΔD86].

5. (Amended) The method according to claim 3, wherein at least one of said first protein or protein domain and said second protein or protein domain [the proteins or protein domains with anti-pathogenic activity is the] comprises CpTI [proteinase inhibitor CpTI].

6. (Amended) The method according to claim 1, wherein [the gene is functionally linked to] said DNA molecule comprises a promoter sequence capable of driving expression preferentially in plant roots.

7. (Amended) The method according to claim 1, wherein the linker peptide comprises an amino acid sequence which is capable of being proteolytically cleaved by the plant.

8. (Amended) The method according to claim 1, wherein the linker peptide

comprises an amino acid sequence which is capable of being proteolytically stable in the plant.

13. (Amended) [A] An isolated DNA molecule [capable of] encoding a fusion [protein comprising] protein, wherein said fusion protein comprises:

(a) a first [protein or protein domain] protein, or protein domain, with anti-pathogenic activity;

(b) a linker peptide; and

(c) a second [protein or protein domain] protein, or protein domain, with anti-pathogenic activity, wherein at least one of the proteins or protein domains with anti-pathogenic activity has proteinase inhibitor activity.

14. (Amended) The DNA molecule according to claim 13 wherein said [the encoded] fusion protein further comprises at least one additional protein or protein domain [further proteins or protein domains with anti-pathogenic activity] fused [thereto] by at least one additional linker peptide to at least one of said first protein or protein domain, said linker peptide, and said second protein or protein domain [linker peptides].

16. (Amended) A transgenic plant expressing [the fusion protein encoded by] the DNA molecule according to claim 13.